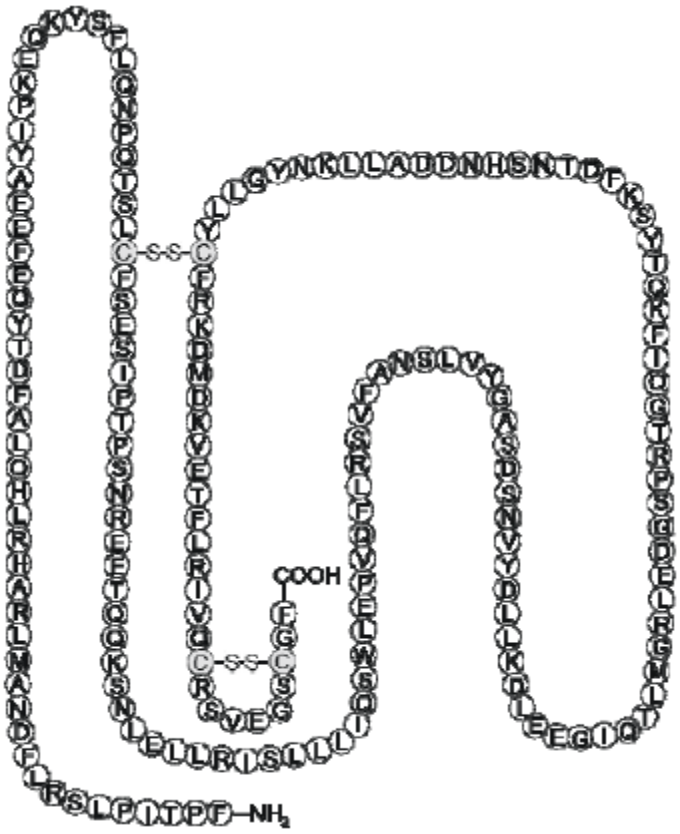
OMNITROPE™
(somatropin [rDNA origin]) for injection

DESCRIPTION

OMNITROPE™ (somatropin [rDNA origin]) for injection is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). OMNITROPE™ is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone. OMNITROPE™ is a sterile white lyophilized powder intended for subcutaneous injection.

Figure 1: Schematic amino acid sequence of human growth hormone including the disulfide bonds



The biological activity of hGH is determined by the rat weight gain bioassay according to the U.S. Pharmacopeial monograph for Somatropin. This bioassay is based on the hGH mediated growth induction in hypophysectomized rats. The bioidentity of the recombinant protein is measured by comparing its growth inducing effect with the growth inducing effect of a reference preparation calibrated in International Units.

OMNITROPE™ 5.8 mg is dispensed in a vial containing 5.8 mg of somatropin (approximately 17.4 IU), glycine (27.6 mg), disodium hydrogen phosphate heptahydrate (2.09 mg), and sodium dihydrogen phosphate dihydrate (0.56 mg). The product is supplied with a vial containing 1.14 mL diluent (Bacteriostatic Water for Injection containing 1.5% benzyl alcohol as a preservative). After reconstitution of the lyophilized powder, the solution has a concentration of 5 mg/mL (approx. 15 IU/mL).

OMNITROPE™ 1.5 mg is dispensed in a vial containing 1.5 mg of somatropin (approximately 4.5 IU), glycine (27.6 mg), disodium hydrogen phosphate heptahydrate (0.88 mg), and sodium dihydrogen phosphate dihydrate (0.21 mg). The product is provided with a vial containing 1.13 mL of diluent (Sterile Water for Injection). After reconstitution of the lyophilized powder, the solution has a concentration of 1.33 mg/mL (approx. 4 IU/mL).

The reconstituted somatropin solution has an osmolality of approximately 300 mOsm/kg, and a pH of approximately 7.0. The concentration of the reconstituted solution varies by strength and presentation (see HOW SUPPLIED section).

CLINICAL PHARMACOLOGY

In vitro, preclinical, and clinical tests have demonstrated that somatropins are therapeutically equivalent to human growth hormone of pituitary origin and achieve similar pharmacokinetic profiles in normal adults. In pediatric patients who have growth hormone deficiency (GHD), treatment with somatropin stimulates linear growth and normalizes concentrations of Insulin-like Growth Factor -I (IGF-I).
In adults with GHD, treatment with somatropin results in reduced fat mass, increased lean body mass, metabolic alterations that include beneficial changes in lipid metabolism, and normalization of IGF-I concentrations.
In addition, the following actions have been demonstrated for OMNITROPE™ and/or somatropin.

1. Tissue Growth
A. Skeletal Growth:
Somatropin stimulates skeletal growth in pediatric patients with GHD. The measurable increase in body length after administration of somatropin results from an effect on the epiphyseal plates of long bones. Concentrations of IGF-I, which may play a role in skeletal growth, are generally low in the serum of pediatric patients with GHD, but tend to increase during treatment with OMNITROPE™. Elevations in mean serum alkaline phosphatase concentration are also seen.

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B. Cell Growth:

It has been shown that there are fewer skeletal muscle cells in short-statured pediatric patients who lack endogenous growth hormone as compared with the normal pediatric population. Treatment with somatropin results in an increase in both the number and size of muscle cells.

2. Protein Metabolism

Linear growth is facilitated in part by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, follows the initiation of therapy with somatropin.

3. Carbohydrate Metabolism

Pediatric patients with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with somatropin. Large doses of growth hormone may impair glucose tolerance.

4. Lipid Metabolism

In GHD patients, administration of somatropin has resulted in lipid mobilization, reduction in body fat stores, and increased plasma fatty acids.

5. Mineral Metabolism

Somatropin induces retention of sodium, potassium, and phosphorus. Serum concentrations of inorganic phosphate are increased in patients with GHD after therapy with somatropin. Serum calcium is not significantly altered by somatropin. Growth hormone could increase calciuria.

6. Body Composition

Adult GHD patients treated with somatropin at the recommended adult dose (see DOSAGE AND ADMINISTRATION) demonstrate a decrease in fat mass and an increase in lean body mass.

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When these alterations are coupled with the increase in total body water, the overall effect of somatropin is to modify body composition, an effect that is maintained with continued treatment.

PHARMACOKINETICS

Absorption
Following a subcutaneous injection of single dose of 5 mg OMNITROPE™ in healthy male and female adults, the extent of absorption (AUC) was 291 hr.μg/L and the peak concentration (Cmax) was 37 μg/L. There are no pharmacokinetic data from patients with GHD.

Distribution
The mean volume of distribution of OMNITROPE™ following administration to healthy adults was estimated to be 1.4 L/kg.

Metabolism
The metabolic fate of OMNITROPE™ was not studied. However, it is presumed that the metabolic fate of OMNITROPE™ involves classical protein catabolism in both the liver and kidneys.

Excretion
The mean clearance subcutaneously administered OMNITROPE™ in healthy adults was 0.23 (± 0.04) L/hr · kg. The mean terminal half-life of OMNITROPE™ after a single subcutaneous injection in healthy adults is 2.4 hours.

Special Populations
Pediatric: Available literature data suggest that GH clearance is similar in GHD pediatric and adult patients.

Gender: No gender studies have been performed in pediatric patients; however, following a subcutaneous injection of 5 mg (around 0.07 mg/kg) OMNITROPE™ to healthy adults volunteers, gender has no effect on some pharmacokinetic parameters of OMNITROPE™ (C_{max} and t_{max}). However, statistical differences were observed for some pharmacokinetic parameters (AUC, Vz, CL/F) of OMNITROPE™ and between males and females, which can be explained by differences in body weight.

Race: No studies have been conducted with OMNITROPE™ to assess pharmacokinetic differences among races.
Renal or hepatic insufficiency: No studies have been conducted with OMNITROPE™ in these patient populations.

CLINICAL STUDIES

Pediatric Growth Hormone Deficiency (GHD)
The efficacy and safety of OMNITROPE™ was compared with another somatropin approved for growth hormone deficiency (GHD) in pediatric patients. In a randomized clinical trial involving a total of 89 GHD children 44 patients received OMNITROPE™ and 45 patients received the other somatropin for 9 months. OMNITROPE™ was continued beyond 9 months on the same treatment and dose. In both groups, somatropin was administered as a daily subcutaneous (SC) injection at a dose of 0.03 mg/kg. OMNITROPE™ and the somatropin comparator showed similar effects on growth during the 9 months of treatment. The efficacy results for OMNITROPE™ are summarized in Table 1.

	OMNITROPE™ N=44[2] Mean (SD)	Somatropin N=45[2] Mean (SD)	Treatment effect1 Mean (95% CI)
Height velocity (cm/yr)			
Pre-treatment	3.8 (1.2)	4.0 (0.8)	
Month 9	10.7 (2.6)	10.7 (2.9)	
Change from pre-treatment to Month 9	6.9 (3.1)	6.8 (3.2)	-0.2 (-1.4, 0.9)
Height velocity SDS			
Pre-treatment	-2.4 (1.3)	-2.3 (1.1)	
Month 9	6.1 (3.7)	5.4 (3.2)	
Change from pre-treatment to Month 9	8.6 (4.2)	7.8 (3.4)	0.6 (-0.8, 2.1)
Height SDS	-3.0 (0.7)	-3.1 (0.9)	
Pre-treatment	-2.3 (0.7)	-2.5 (0.7)	
Month 9	0.8 (0.4)	0.7 (0.5)	0.1 (0.0, 0.3)
Change from pre-treatment to Month 9			
IGF-1[3]			
Pre-treatment	158.6 (92.0)	157.7 (43.0)	
Month 9	291.1 (174.0)	301.9 (182.9)	
IGFBP-3[3]			
Pre-treatment	3.5 (1.3)	3.5 (1.0)	
Month 9	4.6 (3.0)	4.0 (1.5)	

1 Between-group comparison for change from pre-treatment performed using ANCOVA with baseline as the covariate. The treatment effect is expressed as least squares mean (95% CI)
2 Data for month 9 and any differences between pre-treatment and month 9 are only based on patients who completed the study up to month 9, i.e. with OMNITROPE™: N = 42, Somatropin: N = 44.
3 Calculated only for patients with measurements above the level of detection

Subjects in the OMNITROPE™ group were continued on the same treatment for 6 additional months in an extension phase. Height velocity during the extension phase (months 9 to 15) was comparable to height velocity during Months 6-9.

Adult Growth Hormone Deficiency (GHD)
Randomized, placebo-controlled clinical trials with somatropin have been conducted in adult GHD patients.

In these trials, beneficial changes in body composition were observed at the end of a 6-month

treatment period for patients receiving somatropin as compared with the placebo patients. Lean body mass, total body water, and lean/fat ratio increased, while total body fat mass and waist circumference decreased. These effects on body composition were maintained when treatment was continued beyond 6 months. Bone mineral density declined after 6 months of treatment but returned to baseline values after 12 months of treatment.

INDICATIONS AND USAGE

OMNITROPE™ is indicated for:

- Long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone.
- Long-term replacement therapy in adults with growth hormone deficiency (GHD) of either
  childhood- or adult- onset etiology. GHD should be confirmed by an appropriate growth hormone stimulation test.

CONTRAINDICATIONS

OMNITROPE™ should not be used when there is any evidence of neoplastic activity. Intracranial lesions must be inactive and antitumor therapy complete prior to the institution of therapy. OMNITROPE™ should be discontinued if there is evidence of tumor growth.

Growth hormone should not be used for growth promotion in pediatric patients with fused epiphyses.

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental traumas, or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients with these conditions revealed a significant increase in mortality among somatropin-treated patients compared to those receiving placebo (see WARNINGS).

Growth hormone is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment.

Treatment with OMNITROPE™ is contraindicated in case of hypersensitivity to somatropin or to any of the excipients.

WARNINGS

The OMNITROPE™ 5.8 mg presentation contains benzyl alcohol as a preservative. It should not be used in newborns.

See CONTRAINDICATIONS for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental traumas, or with acute respiratory failure. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of

treatment continuation with growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

PRECAUTIONS

General

Treatment with OMNITROPE™, as with other growth hormone preparations, should be directed by physicians who are experienced in the diagnosis and management of patients with GHD.

Patients and caregivers who will administer OMNITROPE™ in medically unsupervised situations should receive appropriate training and instruction on the proper use of OMNITROPE™ from the physician or other suitably qualified health professional.

Patients with GHD secondary to an intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process. Review of literature reports of pediatric use of somatropin replacement therapy reveals no relationship between this therapy and recurrence of central nervous system (CNS) tumors. In adults, it is unknown whether there is any relationship between somatropin treatment and CNS tumor recurrence.

Patients should be monitored carefully for any malignant transformation of skin lesions.

Caution should be used if growth hormone is administered to patients with diabetes mellitus, and insulin dosage may need to be adjusted. Patients with diabetes or glucose intolerance should be monitored closely during treatment with OMNITROPE™. Patients with risk factors for glucose intolerance, such as obesity or a family history of Type II diabetes, should be monitored closely as well. Because growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance.

In patients with hypopituitarism (multiple hormonal deficiencies) standard hormonal replacement therapy should be monitored closely when treatment with OMNITROPE™ is instituted. Hypothyroidism may develop during treatment with OMNITROPE™, and inadequate treatment of hypothyroidism may prevent optimal response to OMNITROPE™. Therefore, patients should have periodic thyroid function tests and be treated with thyroid hormone when indicated.

Pediatric patients with endocrine disorders, including GHD, have a higher incidence of slipped capital femoral epiphyses. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during growth hormone therapy should be evaluated.

Progression of scoliosis can occur in patients who experience rapid growth. Because growth hormone increases growth rate, patients with a history of scoliosis who are treated with growth hormone should be monitored for progression of scoliosis. However, growth hormone has not been shown to increase the incidence of scoliosis.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone products. Symptoms usually occurred within the first 8 weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or

a reduction of the growth hormone dose.

Funduscopic examination of patients is recommended at the initiation, and periodically during the course of growth hormone therapy.

Before continuing treatment as an adult, a post-pubertal GHD patient who received growth hormone replacement therapy in childhood should be reevaluated with proper testing as described in INDICATIONS AND USAGE. If continued treatment is appropriate, OMNITROPE™ should be administered at the reduced dose level recommended for adult GHD patients.

Drug Interactions

Concomitant glucocorticoid treatment may inhibit the growth-promoting effect of growth hormone. Pediatric GHD patients with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth (see also PRECAUTIONS - General.) Limited published data indicate that growth hormone treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that growth hormone administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g. corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when growth hormone is administered in combination with other drugs known to be metabolized by CP450 liver enzymes.

Carcinogenesis, Mutagenesis, Impairment Of Fertility
Mutagenicity or carcinogenicity studies have not been conducted with OMNITROPETM.

Pregnancy: Pregnancy Category B
Reproduction studies carried out with recombinant human growth hormone (somatropin) at doses of 0.3, 1, and 3.3 mg/kg/day administered subcutaneously (SC) in the rat and 0.08, 0.3, and 1.3 mg/kg/day administered intramuscularly in the rabbit (highest doses approximately 24 times and 19 times the recommended human therapeutic levels, respectively, based on body surface area) resulted in decreased maternal body weight gains but were not teratogenic. In rats receiving SC doses during gametogenesis and up to 7 days of pregnancy, 3.3 mg/kg/day (approximately 24 times human dose) produced anestrus or extended estrus cycles in females and fewer and less motile sperm in males. When given to pregnant female rats (days 1 to 7 of gestation) at 3.3 mg/kg/day a very slight increase in fetal deaths was observed. At 1 mg/kg/day (approximately seven times human dose) rats showed slightly extended estrus cycles, whereas at 0.3 mg/kg/day no effects were noted.

In perinatal and postnatal studies in rats, somatropin doses of 0.3, 1, and 3.3 mg/kg/day produced growth-promoting effects in the dams but not in the fetuses. Young rats at the highest dose showed increased weight gain during suckling but the effect was not apparent by 10 weeks of age. No adverse effects were observed on gestation, morphogenesis, parturition, lactation, postnatal development, or reproductive capacity of the offspring due to somatropin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

There have been no studies conducted with somatropin in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when somatropin is administered to a nursing woman.

Geriatric Use
The safety and effectiveness of OMNITROPE™ in patients age 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of OMNITROPE™ and may be more prone to develop adverse reactions.

ADVERSE REACTIONS

As with all protein drugs, a small number of patients may develop antibodies to the protein. Growth hormone antibody with binding capacity lower than 2 mg/L has not been associated with growth attenuation. In some cases when binding capacity is > 2mg/L, interference with growth response has been observed.

Preparations of OMNITROPETM contain a small amount of host cell Escherichia coli peptides (HCP). Anti-HCP antibodies are found in a small number of patients treated with OMNITROPETM, but these appear to be of no clinical significance.

The following events were observed during the OMNITROPETM clinical studies conducted in children with GHD:

Table 2. Incidence of drug-related treatment-emerged adverse events occurring in ≥ 5% pediatric patients with GHD during first 15 months of treatment (N=44)

Adverse event	Number (%)
Hypothyroidism	7 (16%)
Elevated HbA1c	6 (14%)
Eosinophilia	5 (11%)
Hematoma	4 (9%)
Headache	3 (7%)
Hypertriglyceridemia	2 (5%)
Leg Pain	2 (5%)

In clinical trials with somatropin in GHD adults, the majority of the adverse events consisted of mild to moderate symptoms of fluid retention, including peripheral swelling, arthralgia, pain and stiffness of the extremities, peripheral edema, myalgia, paresthesia, and hypoesthesia. These events were reported early during therapy, and tended to be transient and/or responsive to dosage reduction.

The following events were observed in patients using somatropins (see also WARNINGS and PRECAUTIONS sections:
Short-term local injection site reactions, such as pain, numbness, redness and swelling. The subcutaneous administration of growth hormone at the same injection site over a long period may result in local lipoatrophy.
Disturbances in fluid balance (swelling), joint pain, muscle pain, stiffness of the hands and feet, numbness. In general, these undesirable effects occur at the beginning of therapy with growth

hormones and also depend on the dose. They are common in adult patients, but uncommon in children.

Carpal tunnel syndrome in adults.
Benign intracranial hypertension, diabetes mellitus.

Due to the content of benzyl alcohol in OMNITROPE™, rare general hypersensitivity reactions are possible. No case was observed during the clinical trials.

Leukemia has been reported in small number of pediatric patients who have been treated with growth hormone, including growth hormone of pituitary origin and recombinant GH. The relationship, if any, between leukemia and growth hormone therapy is uncertain.

OVERDOSAGE

There is little information on acute or chronic overdosage with OMNITROPE™. Intravenously administered growth hormone has been shown to result in an acute decrease in plasma glucose. Subsequently, hyperglycemia was seen. It is thought that the same effect might occur on rare occasions with a high dosage of OMNITROPE™ administered SC. Long-term overdosage may result in signs and symptoms of acromegaly consistent with overproduction of growth hormone.

DOSAGE AND ADMINISTRATION

The dosage of OMNITROPE™ must be adjusted for the individual patient. The weekly dose should be divided into daily subcutaneous injections (administered preferably in the evening). OMNITROPE™ may be given in the thigh, buttocks, or abdomen; the site of SC injections should be rotated daily to help prevent lipoatrophy.

Pediatric GHD Patients: Generally, a dose of 0.16 to 0.24 mg/kg body weight/week is recommended.

Adult GHD Patients: The recommended dosage at the start of therapy is not more than 0.04 mg/kg/week. The dose may be increased at 4- to 8-week intervals according to individual patient requirements to a maximum of 0.08 mg/kg/week, depending upon patient tolerance of treatment. Clinical response, side effects, and determination of age-adjusted serum IGF-I may be used as guidance in dose titration. This approach will tend to result in weight-adjusted doses that are larger for women compared with men and smaller for older and obese patients.

OMNITROPE™ must not be injected intravenously.

OMNITROPE™ 1.5 mg is supplied with two vials, one containing somatropin as a powder and the other vial containing the diluent (Sterile Water for Injection). A sterile disposable syringe is used to mix the diluent and powder.

OMNITROPE™ 5.8 mg is supplied with two vials, one containing somatropin as a powder and the other vial containing diluent (Bacteriostatic Water for Injection containing benzyl alcohol as a preservative). A sterile disposable syringe is used to withdraw the diluent and then reconstitute the lyophilized powder.

Once the diluent is added to the lyophilized powder, swirl gently; do not shake. Shaking may

cause denaturation of the active ingredient.

All parenteral drug products should be inspected visually for particulate matter and discoloration

prior to administration. If the solution is cloudy, the contents MUST NOT be injected.
Patients and caregivers who will administer OMNITROPE™ in medically unsupervised situations should receive appropriate training and instruction on the proper use of OMNITROPE™ from the physician or other suitably qualified health professional.

STABILITY AND STORAGE

Store OMNITROPE™ refrigerated at 2° to 8°C (36° to 46°F). Do not freeze.
OMNITROPETM is light sensitive and should be stored in the carton.
OMNITROPE™ 1.5 mg is supplied with a diluent without preservative. After reconstitution, the vial may be stored under refrigeration for up to 24 hours. Use once and discard any remaining solution.

OMNITROPE™ 5.8 mg is supplied with a diluent containing benzyl alcohol as a preservative. After reconstitution, the contents of the vial must be used within 3 weeks. After the first injection the vial should be stored in the carton in a refrigerator at 2° to 8°C (36° to 46°F).

HOW SUPPLIED

OMNITROPE™ (somatropin [rDNA origin]) for Injection 1.5 mg/vial
After reconstitution, the concentration is 1.33 mg/mL (approximately 4 IU/mL).
Carton contains 1 vial of OMNITROPETM 1.5 mg and 1 vial of diluent (Sterile Water for Injection).

NDC 43858-700-01

OMNITROPE™ (somatropin [rDNA origin]) for Injection 5.8 mg/vial
After reconstitution, the concentration is 5 mg/mL (approximately 15 IU/mL).
Carton contains 8 vials of OMNITROPETM 5.8 mg and 8 vials of diluent (Bacteriostatic Water for Injection containing 1.5% benzyl alcohol as a preservative.)

NDC 43858-701-01
Rx only

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